How Are Emerging PM Susceptible Populations Being Identified and Characterized?

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Science Questions

The overall weight of evidence from panel, clinical, and toxicological studies has demonstrated the ability of ambient PM exposure to induce a variety of extra-pulmonary health effects ranging from alterations in hematological parameters to cardiac function. PM mechanistic studies have shown the systemic release of particle associated constituents and ultrafine particles following their pulmonary deposition. These findings raise the following science questions:

-Do additional susceptible subpopulations exist due to the ability of pulmonary deposited PM to release its constituents and induce systemic toxic effects?

-What are the sensitivity factors, or effect modifiers, within newly identified PM susceptible subpopulations?

-What are the PM properties and mechanism(s) of injury responsible for adverse health effects within newly identified susceptible subpopulations?

Research Goals

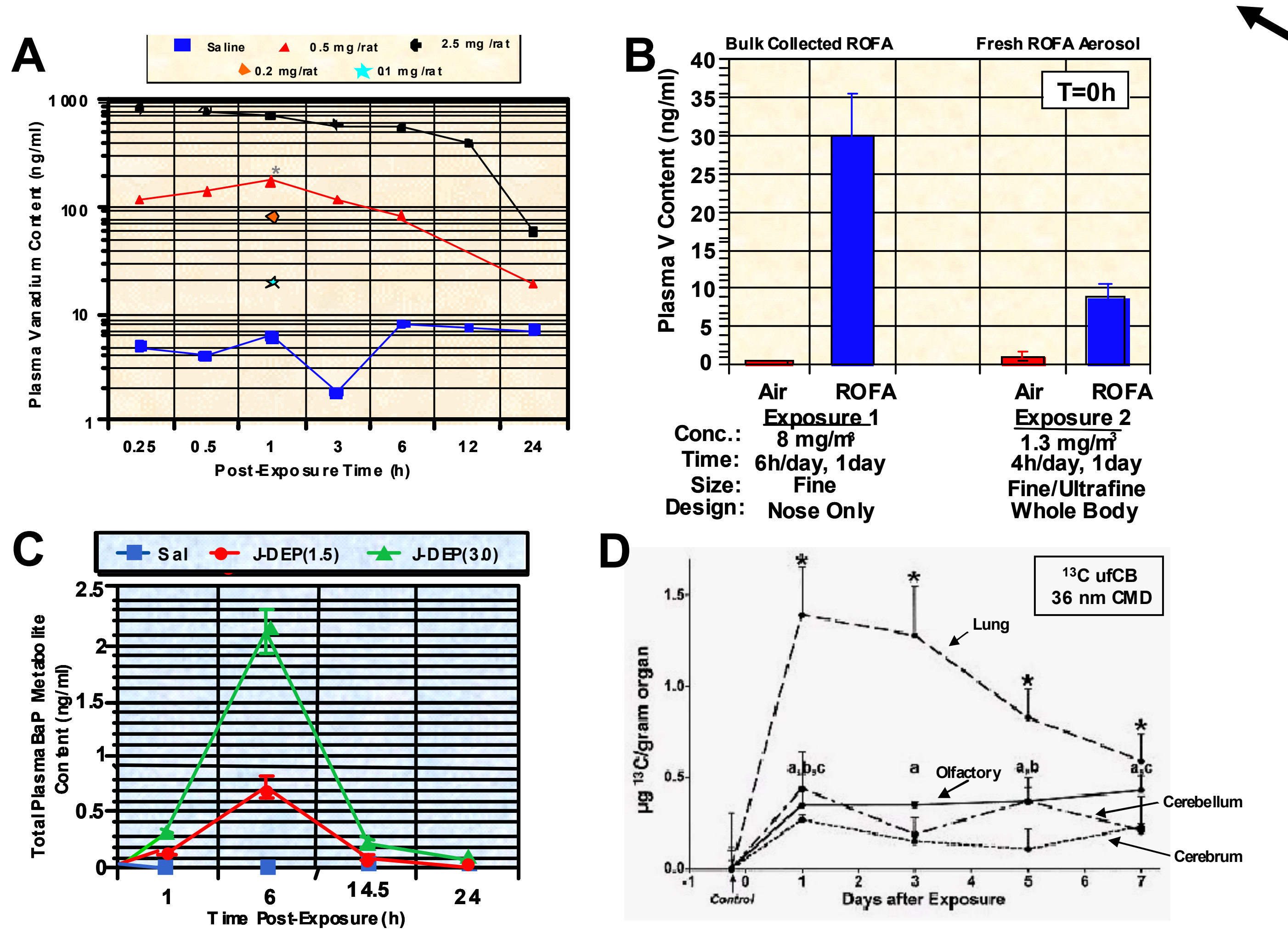
Integrated epidemiological, clinical and toxicological research efforts will be conducted to:

-better identify and characterize populations of individuals at high risk to adverse health effectsassociated with short and long term PM exposures

-identify PM properties responsible for adverse health effects within newly identified susceptible subpopulations in order to link health effects to sources

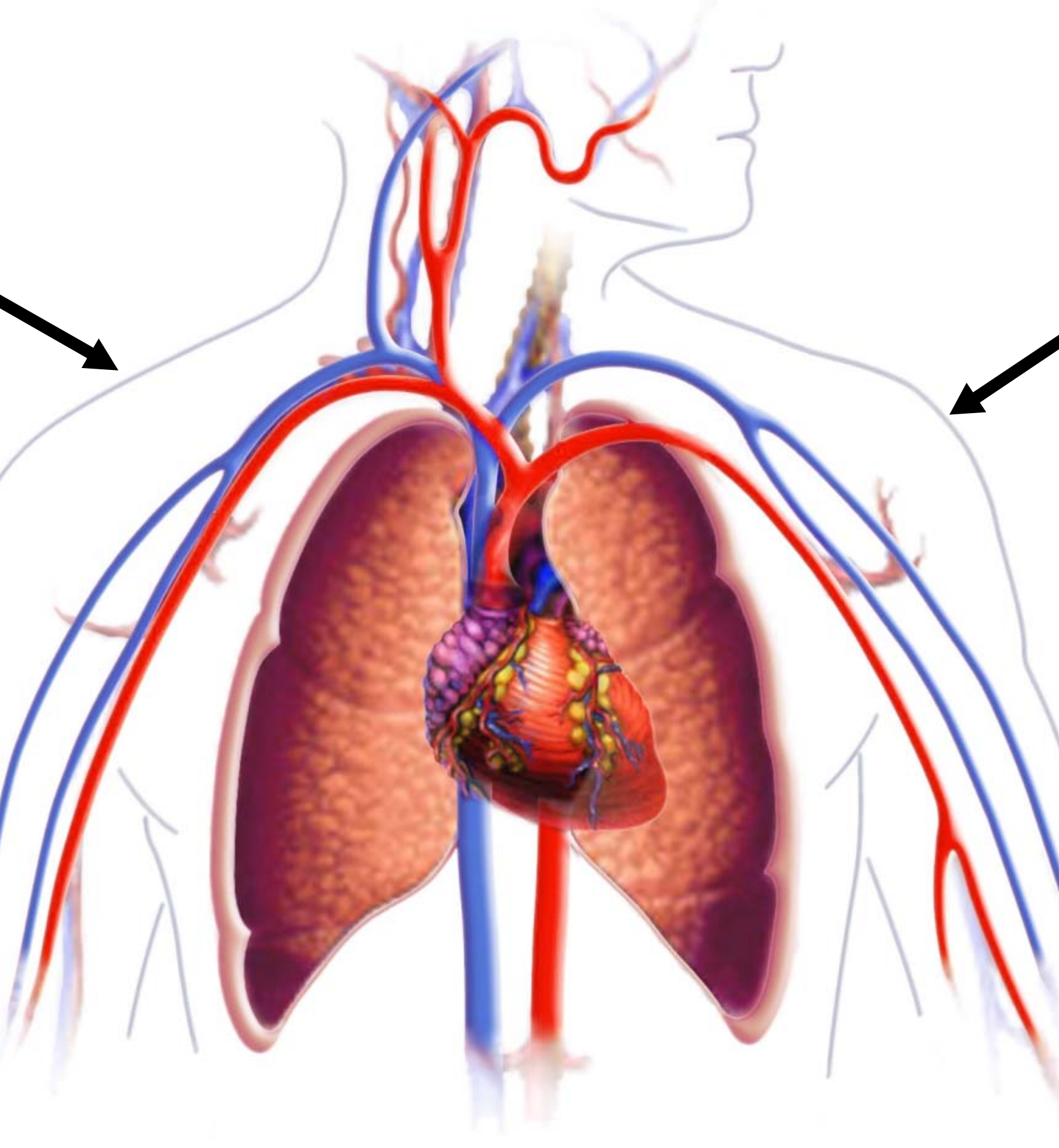
-determine the mechanism(s) and dose-response relationships associated with the adverse health effects observed in newly identified PM susceptible subpopulations

Exposure: Systemic Delivery of PM Constituents



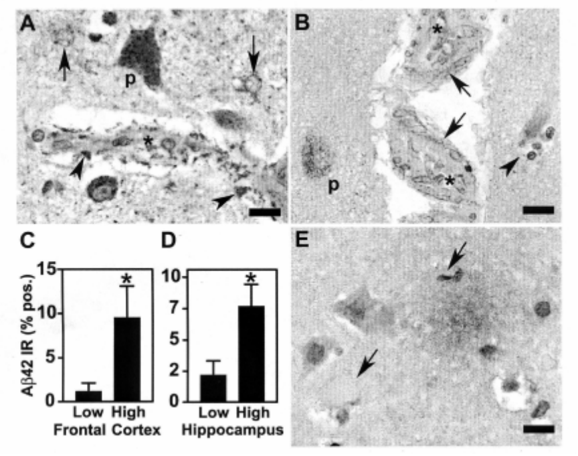
Toxicology Studies: Pulmonary deposition of oil combustion particles (ROFA), by either intratracheal instillation (IT) (A) or inhalation (B), and diesel exhaust particles (C), by IT, leads to a rapid elevation of particle associated constituents in the plasma of exposed rats. (D) Particles translocate to the brains of animals following inhalation to ultrafine carbon black particles.

Approach/Methods/Results



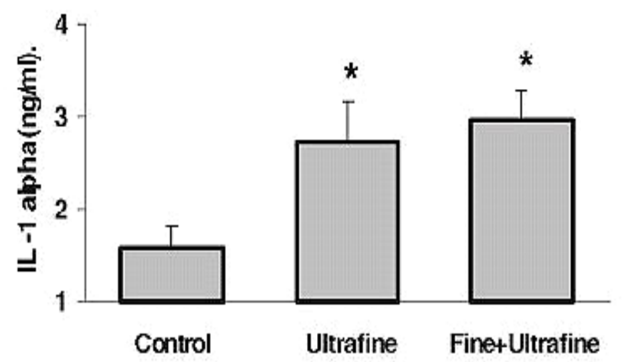
PM Exposure Effects Other Susceptible Populations

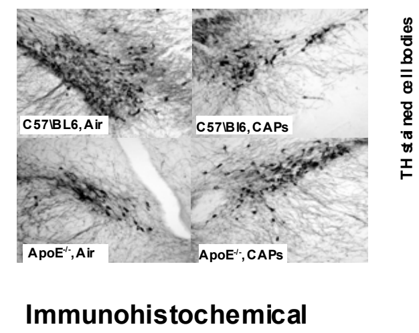
Neurological Effects: Alzheimer's, Dementia



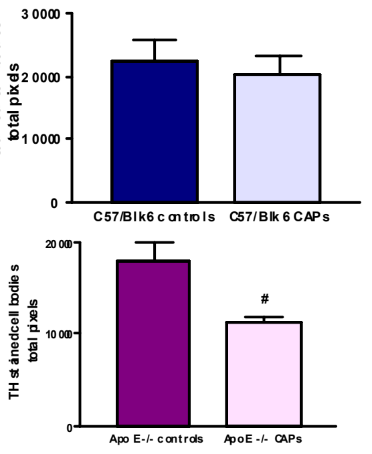
Clinical Study: Elevated levels of Aβ12, a neurotoxic fragment of the amyloid precursor protein (APP), which causes neuronal dysfunction, is observed in various cellular locations in human brain tissues recovered from individuals living in urban areas of high air pollution.

Toxicology Study: Exposure to concentrated ambient air $PM_{2.5}$ increases pro-inflammatory mediator expression in the brain tissue of exposed mice.



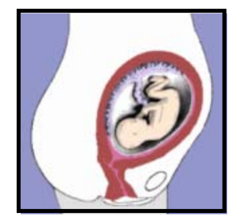


Immunohistochemical staining of dopaminergic neurons with anti-tyrosine hydroxylase Ab.



Toxicology Study: Exposure to concentrated ambient air $PM_{2.5}$ decreases neuronal cells in cardiovascular compromised but not healthy mice.

Reproductive Effects: Premature Births, Birth Defects, Low Birth Weights



Epidemiology Study: Seven County Study of Air Quality and Births, Texas, 1997-2000
Result: An association between PM_{10} and atrial septal defects was observed when comparing high vs. low quartiles of exposure (OR=2.27; 95% CI:1.43, 3.60)

Epidemiology Study: A Time Series Analysis of Air Pollution and Preterm Birth in Pennsylvania, 1997-2001
Result: Increased risk for preterm delivery with exposure to:
- PM_{10} in the 6 weeks before birth, RR=1.07, 95% CI: 0.98-1.18 per 50 µg/m³;
- PM_{10} 2 and 5 days before birth, RR=1.10, 95% CI:1.00-1.21 and RR=1.07, 95% CI:0.98-1.18, respectively.

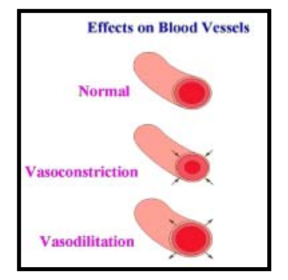
Table 1
Mean Birth Weight and Percentage SGA by Quartile of Nine-Month $PM_{2.5}$ Exposure

QUARTILES OF EXPOSURE	BIRTH WEIGHT OUTCOME	
	SGA, %	Birth Weight (mean g)
$PM_{2.5}$ µg/m³		
<11.9	8.5	3528
11.9-13.9	7.5	3544
13.9-18.4	8.4	3517
>18.4	9.2	3502
	P=0.04	*P<0.001*

SGA, small for gestational age

Exposure to Elevated Levels of Ambient Air PM is Associated With Premature Births, Birth Defects, and Low Birth Weights

Vascular Effects: Diabetes



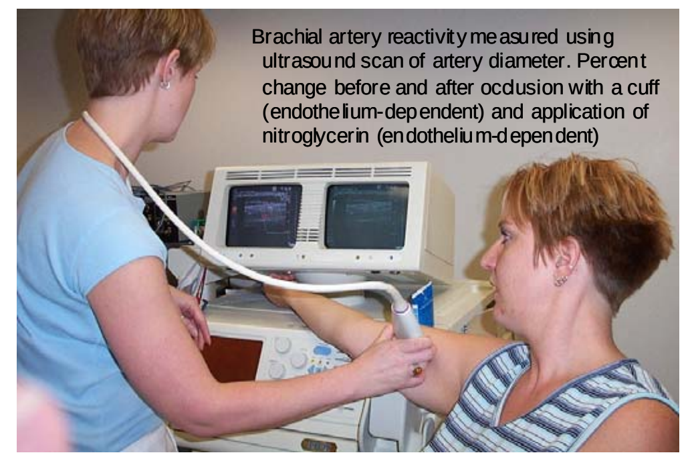
Epidemiology Study: Diabetics have double the risk of a PM_{10}-associated cardiovascular admission when compared to non-diabetics. Persons 75 years of age and older have higher risks. Diabetics are a particularly susceptible population to the adverse health effects of air particulate pollution.

Table 2. Diabetics Are More Susceptible to PM Morbidity

AGE	DIABETES			
	WITH		WITHOUT	
	%	95% CI	%	95% CI
In all cities*				
Young	1.6	1.2-2.0	0.9	1.2-2.0
Old	2.0	1.6-2.4	1.3	1.0-1.5
In three cities (excluding Chicago)	1.5	1.0-2.0	0.9	0.6-1.3
Young	1.9	1.3-2.4	1.3	1.0-1.6
Old				

*, Chicago, Detroit, Pittsburgh, Seattle

Type 2 Diabetics Are More Susceptible to PM-Induced Alterations in Vascular Function



Brachial artery reactivity measured using ultrasound scan of artery diameter. Percent change before and after occlusion with a cuff (endothelium-dependent) and application of nitroglycerin (endothelium-dependent)

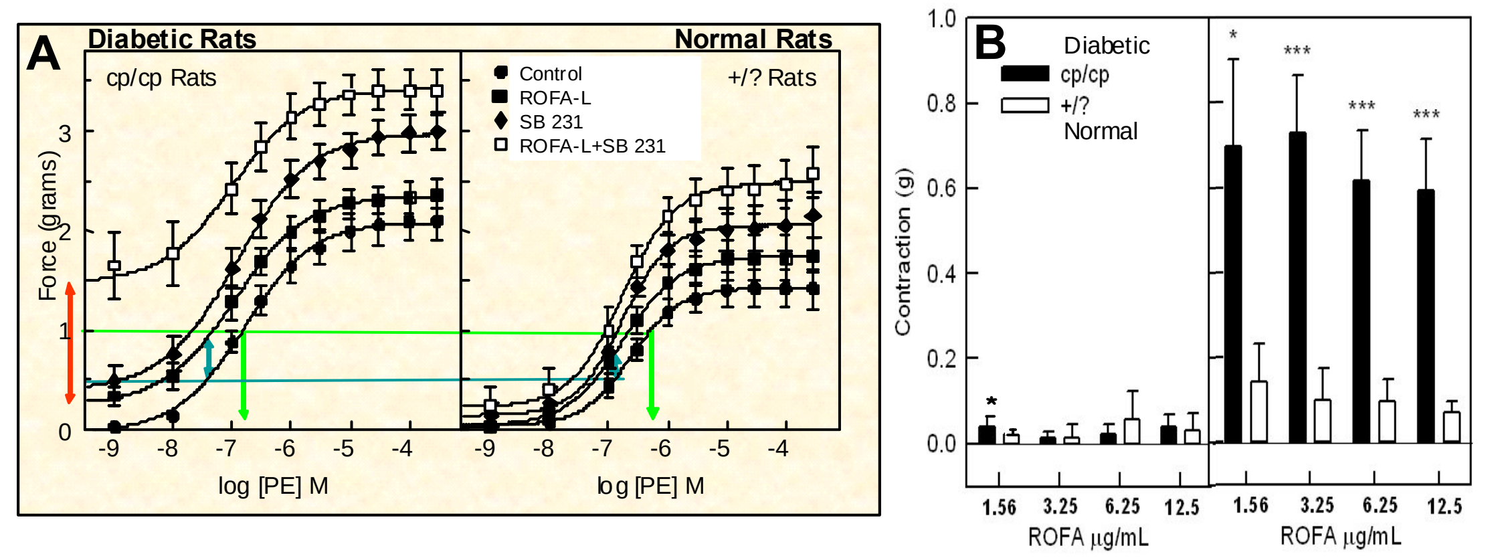
Subjects with Type 2 diabetes had reduced vascular reactivity on higher pollution days, notably with sulfate particles. The association was opposite for those at risk.

Associations between 6-day moving average exposure to particulate air pollutants and vascular reactivity, controlling for age, race, sex, BMI*, season, apparent temperature, and disease status (for total subjects estimate)

Subjects	Pollutant	n	Endothelium dependent % change per IQR † (95% CI ‡)	n	Endothelium independent % change per IQR (95% CI)
Total	Black carbon	234	-9.3 (-17.8, 0.2)	217	-5.4 (-12.0, 1.7)
	$PM_{2.5}$ §	269	-6.2 (-13.0, 1.0)	251	-6.2 (-11.0, -1.1)
	Particle #	211	1.2 (-14.0, 19.1)	196	-1.5 (-12.9, 11.4)
	Sulfate	210	-9.0 (-14.9, -2.7)	197	-4.5 (-9.1, 0.3)
At risk	Black carbon	42	23.9 (-9.7, 69.8)	39	-2.0 (-20.9, 21.3)
	$PM_{2.5}$	42	8.0 (-15.9, 38.8)	39	0.7 (-14.1, 18.1)
	Particle #	42	28.7 (-14.1, 92.7)	39	45.8 (4.5, 103.4)
	Sulfate	40	1.7 (-15.6, 22.6)	38	-2.0 (-14.3, 12.0)
All diabetes	Black carbon	192	-12.6 (-21.7, -2.4)	178	-6.6 (-14.0, 1.5)
	$PM_{2.5}$	227	-7.6 (-14.9, 0.4)	212	-7.6 (-12.8, -2.1)
	Particle #	169	-5.6 (-20.7, 12.5)	157	-9.2 (-20.1, 3.2)
	Sulfate	170	-10.7 (-17.3, -3.5)	159	-5.4 (-10.5, -0.1)
Type 2	Black carbon	148	-12.8 (-23.5, -0.6)	135	-6.8 (-15.1, 2.4)
	$PM_{2.5}$	183	-8.8 (-17.0, 0.1)	169	-8.5 (-14.1, -2.5)
	Particle #	125	-6.3 (-24.5, 16.2)	114	-11.1 (-23.8, 3.8)
	Sulfate	125	-12.1 (-19.3, -4.2)	115	-6.2 (-11.5, -0.6)
Type 1	Black carbon	45	2.8 (-19.7, 31.8)	44	-4.2 (-22.9, 19.2)
	$PM_{2.5}$	45	1.0 (-17.4, 23.5)	44	-4.8 (-19.9, 13.1)
	Particle #	44	-1.2 (-28.0, 35.4)	43	-4.8 (-26.9, 24.0)
	Sulfate	45	-4.3 (-25.0, 22.2)	44	-2.2 (-19.8, 19.4)

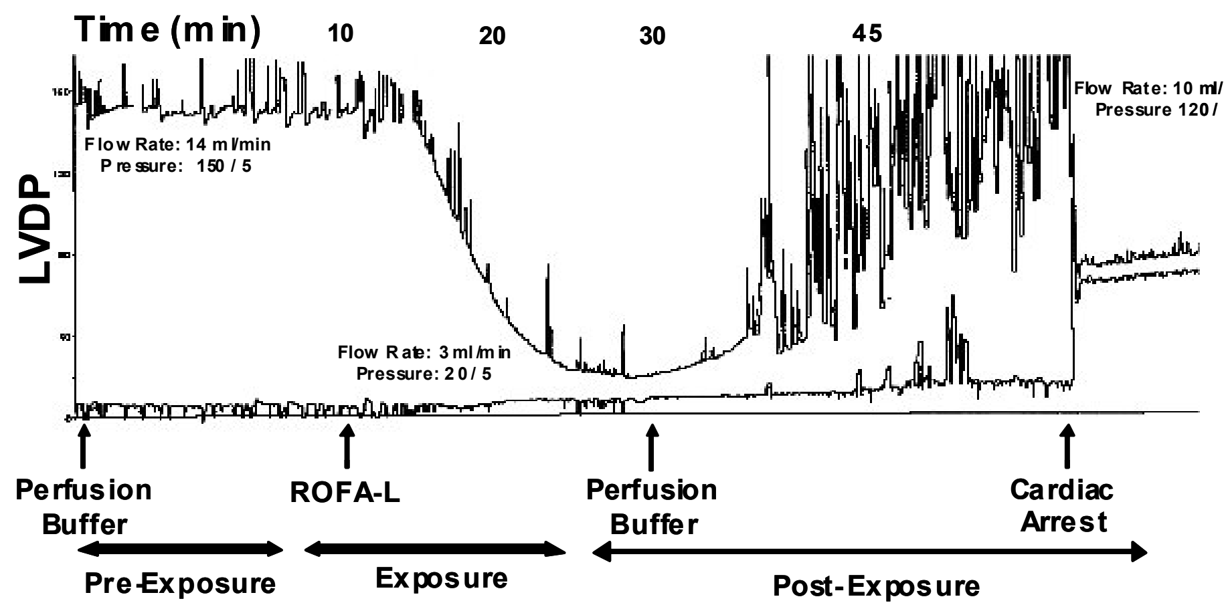
* Body mass index
† Interquartile range of the pollutant, for the days under consideration
‡ confidence interval

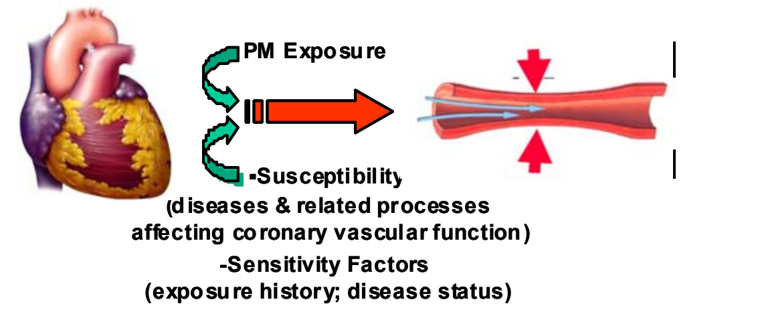
Clinical Study: Particle exposure, including $SO4^{-2}$ and BC, from coal burning power plants and traffic, was associated with decreased vascular reactivity among people with diabetes, but not those at-risk.



Toxicology Studies: Panel A, Consistent with epidemiology and clinical studies, bioavailable constituents of oil combustion particles induce more vasoconstriction in diabetic aortic rings. Inhibition of NOS activity (SB 231) exacerbated this response only in diabetic aortic rings. Panel B, vascular hyperreactivity was observed in diabetic aortic rings following constriction\dilation and a second exposure to ROFA indicating that disease status and exposure history are critical components that regulate the extent of vasoconstriction in diabetic aortas.

Coronary Vascular Effects: Cardiac Spasms, Sudden Cardiac Death, Idiopathic Myocardial Infarction





Toxicology Study: *Ex vivo* exposure of healthy rat hearts to soluble constituents of residual oil combustion particles (ROFA) produces ischemia, arrhythmia and cardiac arrest as observed *in vivo*. This finding provides evidence that PM bioavailable constituents could directly affect coronary vasculature function with fatal consequences especially in individuals with altered or impaired vascular function.

Future Directions

Integrated epidemiological, clinical, and toxicological research efforts are needed to:

-ensure that susceptible subpopulations are identified and characterized with respects to the adverse health effects associated with short and long term PM exposures;

-identify PM properties responsible for adverse health effects within newly identified susceptible subpopulations in order to link health effects to sources;

-determine the mechanism(s) and dose-response relationships associated with the adverse health effects observed in newly identified PM susceptible subpopulations.

Impact

Table 3
Economic Impact of Disease

DISEASE (RELATED SYNDROME)	POPULATION EFFECTED (# in million)	COSTS (Health Care; Prevention; Research; Lose of Productivity) ($ in billion)
Heart Disease (Metabolic Syndrome)	70.1 (47)	$393.5
Type 2 Diabetes[1] (Impaired Glucose Metabolism)	18 (20)	$132.8
Obesity[1]	135	$133
Alzheimer	4.5	$100.7
Premature Births	0.48	$1.2
Birth Defects[2,3]	0.15	$8
Total	228.23 (67)	$769.2

1. Diabetes and Obesity (70% of whom become diabetic) are reaching epidemic levels.
2. National Research Council estimates 3% are related to environmental factors.
3. Birth defects have risen 27% since 1981.

This research will identify additional PM susceptible subpopulations as well as link sources to adverse PM health effects within these groups. This information is critically needed by the Agency in order to:

1) set PM standards based on sound science that protect the most sensitive populations, as mandated by the Clean Air Act; and
2) implement control strategies that decrease levels of causal PM sources. In addition, this research could provide a significant savings in health care costs associated with diseases listed in Table 3 by determining the impact of PM on the progression and\or exacerbation of these diseases and setting standards that provide adequate protection.

Health and Exposure